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Pharmacologic regimens for knee osteoarthritis prevention: Can they be cost-effective?

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Abstract

Objective—We sought to determine the target populations and drug efficacy, toxicity, cost, and initiation age thresholds under which a pharmacologic regimen for knee osteoarthritis (OA) prevention could be cost-effective.

Design—We used the Osteoarthritis Policy (OAPol) Model, a validated state-transition simulation model of knee OA, to evaluate the cost-effectiveness of using disease modifying OA drugs (DMOADs) as prophylaxis for the disease. We assessed four cohorts at varying risk for

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CONFLICT OF INTEREST

The authors do not have any conflict of interest with respect to the content of this paper.

AUTHOR CONTRIBUTIONS

Conception and design: Losina, Katz
Analysis and interpretation of the data: Losina, Burbine, Suter, Hunter, Solomon, Daigle, Dervan, Jordan, Katz
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developing OA: (1) no risk factors, (2) obese, (3) history of knee injury, and (4) high-risk (obese with history of knee injury). The base case DMOAD was initiated at age 50 with 40% efficacy in the first year, 5% failure per subsequent year, 0.22% major toxicity, and annual cost of $1,000. Outcomes included costs, quality-adjusted life expectancy, and incremental cost-effectiveness ratios (ICERs). Key parameters were varied in sensitivity analyses.

Results—For the high-risk cohort, base case prophylaxis increased quality-adjusted life-years (QALY) by 0.04 and lifetime costs by $4,600, and produced an ICER of $118,000 per QALY gained. ICERs >$150,000/QALY were observed when comparing the base case DMOAD to the standard of care in the knee injury only cohort; for the obese only and no risk factors cohorts, the base case DMOAD was less cost-effective than the standard of care. Regimens priced at $3,000 per year and higher demonstrated ICERs above cost-effectiveness thresholds consistent with current US standards.

Conclusions—The cost-effectiveness of DMOADs for OA prevention for persons at high risk for incident OA may be comparable to other accepted preventive therapies.

Keywords

disease-modifying osteoarthritis drugs; knee osteoarthritis; prophylaxis; cost-effectiveness

Introduction

Knee osteoarthritis (OA) is a prevalent disease characterized by chronic pain and functional limitation. Affecting nearly 9.3 million American adults and accounting for $27 billion annually in aggregate health care expenses in the US, the burden of knee OA on our country's population and resources is profound[1,2]. With an increasing proportion of older adults in the country, an obesity epidemic, and the growing prevalence of knee injuries, the growth of this clinical and economic burden shows few signs of slowing down[3–6].

Determining effective means of treating knee OA has become an important subject of study, particularly because currently there is no medical treatment to reverse or stop the progression of OA. Analyses evaluating a role of pharmacologic prevention of knee OA have yet to appear in published literature, even though the development of pharmacologic regimens aimed at preventing incident knee OA has been posed as an important research priority[7,8]. This lack of effective pharmacologic prophylaxis for persons at high risk for knee OA represents a critical gap in the current set of therapeutic options[11].

We sought to conduct an evaluation of pharmacologic prophylaxis as a method of preventing the occurrence of symptomatic knee OA in populations at varying levels of risk for the development of the disease. Using a novel model-based approach that parallels our previous analysis on the cost- effectiveness of DMOADs for knee OA treatment[9], we varied the efficacy, toxicity, cost, and age of initiation associated with the pharmacologic regimen in order to determine the conditions under which -- and the patients for whom -- the use of prophylactic DMOADs may be cost-effective.

Methods

Analytic Overview

We used the Osteoarthritis Policy (OAPol) Model, a validated computer simulation model of knee OA natural history and management, to examine the cost-effectiveness of DMOADs used for knee OA prevention in persons with established knee OA risk factors: obesity and history of knee injury[10–12]. We considered four cohorts: 1) a 'no risk factors' cohort that was non-obese and had no history of knee injury, 2) an 'obese only' cohort in which all subjects were obese but did not have a history of knee injury, 3) a 'knee injury only' cohort in which all subjects had a history of knee injury but were non-obese, and 4) a 'high-risk' cohort where subjects were both obese and had a history of knee injury. Each cohort was initialized with no knee OA at baseline. We varied the age of DMOAD initiation from 30 to 60 years. We established the levels of efficacy, toxicity, and cost required for prophylactic DMOADs to reach specific cost-effectiveness thresholds.

The primary outcomes were quality-adjusted life expectancy (QALE) and lifetime medical costs. Cost-effectiveness for each pharmacologic prevention strategy was then assessed by calculating incremental cost-effectiveness ratios (ICERs, or the ratios of a change in cost over a change in QALE) between strategies undergoing and not undergoing the preventative DMOAD regimen. In accordance with the Recommendations of the US Panel on Cost-Effectiveness in Health and Medicine, costs and quality-adjusted life-years (QALY) were discounted at 3% per year[13]. Strategies that resulted in an increase in cost with a decrease in QALE were labeled "Dominated."

The OAPol Model

The OAPol Model is a validated, state-transition computer simulation model of the natural trajectory and management of knee OA[14,15]. The model operates as a Monte Carlo simulation with annual cycles that draws subjects from user-defined distributions for demographic (e.g. age, sex, and race) and clinical (e.g. body mass index (BMI), knee OA incidence and severity, and the incidence of comorbidities) characteristics. Obesity was defined as having a BMI of greater than or equal to 30kg/m^2 and varied in the model according to a subject's current BMI, age, sex, and race/ethnicity. History of knee injury was incorporated into the model using relative risks for incident knee OA following knee injury reported in published literature[12]. Comorbidities considered by the model included cancer, coronary heart disease (CHD), chronic obstructive pulmonary disorder, diabetes mellitus, and non-OA musculoskeletal disorders. Prevalence and incidence rates for all diseases were dependent on the subject's age, race, sex, and obesity status[16–18]. Cancer, CHD, and obesity each had associated relative risks of mortality; the derivation of this relative risk of mortality due to cancer, CHD, and obesity has been previously published[15]. Underlying mortality rates were derived from 2006 CDC life tables[19].

The model tracks every subject until death, allowing them to transition between health states defined by knee OA severity, the presence of knee pain, obesity, and comorbidities[14,15]. As subjects pass through these health states, they accumulate costs associated with OA-related and non-OA related medical care (in 2012 USD) as well as changes in quality of life (QOL)

that affect a subject's QALE. Annual medical costs not attributable to OA were determined by a subject's number of comorbidities, age, and pain status. Annual QOL estimates were formulated in terms of preference-based measures of utility ranging from 0.0 to 1.0, with 1.0 representing perfect health and 0.0 representing death[20]. The data for baseline QOL were derived from NHANES 2005–08 using the Diehr transformation and from Losina et al. in 2009[17,18,21,22]. Values for QOL utilities were stratified according to obesity status, pain status, age, and the number of comorbidities; previous knee injury was not incorporated into baseline QOL. Further details on the OAPol Model are published elsewhere[9,14,15,23].

Cohort Characteristics

Our analysis evaluated the use of prophylaxis in four hypothetical cohorts characterized by varying degrees of risk for the development of symptomatic knee OA: 'no risk factors' (non-obese and no history of knee injury), 'obese only' (obese and no history of knee injury), 'knee injury only' (history of knee injury and non-obese), and 'high-risk' (both obese and with history of knee injury). Each cohort was initialized with a mean age of 27.5 years (standard deviation 0.83 years). The 2009 US Census indicated that 49% of this age group was female, 64% were non-Hispanic White, 20% were Hispanic, and 16% were non-Hispanic Black[24].

Annual direct medical costs ranged from $1,302 for people ages 25 to 34 with 0 or 1 comorbidities to $18,673 for persons over the age of 80 with greater than 3 comorbidities[17,18,25,26]. We incorporated an additional annual cost of $204 for subjects in pain both on and off regimens to manage OA to account for the cost of pain medication[26,27]. QOL utilities ranged from 0.96 for individuals who were not obese, had 0–1 comorbidities, and experienced no OA pain to 0.66 for individuals who were obese, had 4–5 comorbidities, and were in pain. All subjects with advanced knee OA, defined as a Kellgren-Lawrence (K-L) radiographic grade of 3 or 4, were assigned an annual weighted utility of 0.690[22]. All cost and QOL utility values are presented in Table 1.

OA Incidence—We stratified annual knee OA incidence rates by both obesity status and history of previous knee injury. Base OA incidence rates were derived from OA prevalence data from the National Health Interview Survey (NHIS) 2007–2008 stratified by non-obese and obese populations[16,28]. To account for the impact of previous knee injury on OA incidence, we stratified our cohorts according to our derivations of the prevalence of knee injury in the general population using NHANES 2003–04 data[29]. We then adjusted OA incidence rates with a relative risk of knee OA incidence due to knee injury published by Wilder et al. (8.3 for males and 7.2 for females)[12]. Our incidence rates stratified by obesity and previous knee injury were then further stratified by age and sex; these estimates are presented in Table 1.

Regimens for Prophylaxis and OA Treatment

In this analysis, we evaluated the cost-effectiveness of using DMOADs compared to the use of no prophylactic regimen for the prevention of symptomatic knee OA. Figure 1 provides a basic outline of the health states and treatment sequence experienced by subjects undergoing a DMOADs regimen and subjects undergoing the standard of care, or no prophylaxis. All

subjects entered the model without OA. Following the diagnosis of symptomatic knee OA, OA pain was managed with a series of nonsurgical and surgical regimens described in greater detail under *Guideline-Concordant OA Care*. Prophylaxis was discontinued for those diagnosed with knee OA. The preventative DMOAD regimen and standard of care regimens contributed to changes in costs and QALE over time in the model. Beyond the impact of these regimens on cost and QOL, these regimens had associated risks of toxicity. In the incidence of an adverse event, subjects were evaluated for whether or not the incurred toxicity was major or minor. For example, while subjects had a little over 24% chance of incurring any toxicity due to corticosteroid injections[30], 99.995% of these toxicities were minor (e.g. flare) and 0.005% were major (e.g. sepsis). Thus in all subjects, 24%[31] had a minor toxicity and 0.0013%[32] had a major toxicity in one year of treatment. Medical costs and decrements to a subject's health-related QOL were substantially greater for major adverse events, which imparted an increased risk of mortality.

Subjects discontinued use of the pharmacologic prophylaxis when any of the following occurred: 1) death, 2) diagnosis of symptomatic knee OA, or 3) major toxicity. DMOAD efficacy was defined by a reduction in OA incidence. Notably, undiagnosed incident radiographic OA did not constitute termination from the prevention regimen; subjects continued to incur annual costs and minor toxicities until the development of symptomatic pain and the subsequent observation of the disease. The model evaluated efficacy in the first year of OA prevention as well as the probability that an efficacious regimen would fail in subsequent years (defined as late failure). Late failure could arise due to lack of adherence, tolerance, or other mechanisms. While major toxicity led to a subject's removal from the preventative regimen, minor toxicity did not result in DMOAD discontinuation and had no impact on its likelihood of preventing OA in subsequent years (Figure 2).

Base Case DMOAD Characteristics—In line with recommendations made by the Panel in Cost-effectiveness Analyses in Health and Medicine, we created a 'base case' DMOAD regimen to evaluate the combination of drug efficacy, cost, toxicity, and age of initiation that would be most likely observed in a clinical setting (these are summarized in Table 1)[33]. For this analysis, we assumed a base case prophylaxis regimen with an initiation age of 50 and a 40% probability of preventing OA incidence in the first year. For those who experienced this early efficacy, we assumed that 5% of subjects would experience late failure and thus develop knee OA in subsequent years. We assumed the risk of major toxicity from prophylaxis would be about half of the risks associated with NSAIDs, giving our base case a 0.22% annual probability of major toxicity[34]. For our base case, we settled on $1,000 as a mid-range annual cost based on the annual cost of an NSAID prescription[26].

Guideline-Concordant OA Care—Following OA incidence in the model, subjects became eligible to receive guideline-concordant care to manage knee OA-related pain. These subjects received a sequence of pain management interventions (Figure 1): Regimen 1 (physical therapy, assistive devices, NSAIDs, and acetaminophen), Regimen 2 (intra-articular corticosteroid injections), Regimen 3 (primary total knee replacement, or TKR), and Regimen 4 (revision TKR)[35–39]. Subjects became eligible for each regimen upon the failure of the subsequent regimen in the sequence; uptake of the next regimen was defined

by eligibility, offer, and acceptance rates. Data describing the efficacy, toxicity, and annual costs associated with these knee OA management strategies for first and subsequent years of treatment were derived from literature and are presented in reports published previously by these authors[9,15]. Costs ranged from $437 for corticosteroid injections[26,27,40] to $24,631 for revision TKR[40–42]. Pain relief in the first year ranged from 64% for NSAIDs and corticosteroid injections[27,43] to 86% for primary TKR[44,45]. The likelihood of treatment-associated toxicities ranged from 3.33% for NSAIDs[34,46–48] to 24% for corticosteroid injections[30].

Sensitivity Analyses

To address uncertainty in our assumptions regarding key DMOADs characteristics, in concordance with recommendations of the US Panel on Cost-Effectiveness in Health and Medicine and the International Society for Pharmacoeconomics and Outcomes Research Task Force on Good Modeling Practice, we conducted multilevel deterministic sensitivity analyses[49]. These analyses provide insight into the impact of uncertainty and highlight scenarios in which small changes in model input data produce large changes in model results.

To determine the impact of efficacy, major toxicity, annual cost, and age of initiation on the cost-effectiveness of a preventative DMOAD regimen for knee OA, we conducted a series of two-way sensitivity analyses using a range of values for each DMOAD characteristic (ranges listed in Table 1).

We varied early efficacy from 30% to 70% and late failure from 1% to 10% given that the prophylaxis was efficacious in the first year. Because knee OA incidence is dependent on subject age, we evaluated the impact initiating the DMOAD regimen in subjects aged 30 to 60 in 10-year increments. DMOAD initiation at a younger age potentially generates higher cumulative costs while exposing subjects to drug toxicities for a longer period of time. However, later initiation potentially misses a tangible number of OA cases, especially in high-risk groups. Only those who had not been diagnosed with symptomatic knee OA were eligible for the DMOAD regimen at the given age.

To evaluate the impact of prophylaxis toxicity, we varied annual DMOAD major toxicity from none to 0.44%, a level consistent with the toxicity of selective NSAIDs[34]. Major toxicity accounted for potential upper gastrointestinal complications, and carried a probability of death of 2.93%[50]. We did not consider cardiovascular toxicities because drugs with such adverse events would not likely be used in a prophylactic setting. DMOAD minor toxicity (dyspepsia, diarrhea, rash, etc) was derived from the toxicity associated with non-selective NSAIDs; risk of minor toxicity in the first and subsequent years of the regimen at 9.50% and 7.27%, respectively[43,46]. We assumed major gastrointestinal toxicity from prophylaxis had an associated cost of $9,408[50], while minor toxicity had an associated cost of $47[51].

DMOAD cost for knee OA prophylaxis was based on the cost of antihypertensives (approximately $400 annually for generics)[52,53], cholesterol-lowering agents (approximately $600 annually for generics)[54], and NSAIDS (approximately $1,000 annually, on average)[26].

We considered low- and high-cost scenarios in our sensitivity analyses, varying the annual cost of the DMOAD regimen from $300 to $3,000 per year (Table 1). In addition to considering costs of the DMOAD and its associated toxicities, we accounted for two office visits in the first year ($224 total) and one office visit in every subsequent year ($93), as well as one x-ray in the first year ($41) of the regimen[40,55]. For all costs related to the DMOADs regimen, including medication costs, follow-up visits, and x-rays, we made the conservative assumption that costs would be incurred in the system even in the case of imperfect adherence.

RESULTS

Base Case Analysis

Clinical Benefits of DMOADs Regimen—In the absence of a preventative DMOAD regimen, using current standard of care practices led to an estimated discounted QALE of 25.0 QALYs for the ‘non-obese without knee injury’ cohort (undiscounted: 49.5 QALYs), 23.5 QALYs for the ‘obese only’ cohort (undiscounted: 45.7 QALYs), 24.5 QALYs for the ‘knee injury only’ cohort (undiscounted: 48.2 QALYs), and 22.7 QALYs for the ‘obese with knee injury’ cohort (undiscounted: 43.8 QALYs).

For the high risk ‘obese with knee injury’ cohort, all DMOAD scenarios showed an increase in QALE over the standard of care. The base case preventative DMOAD increased discounted QALE by 0.04 QALYs (undiscounted: 0.13 QALYs) from the standard of care.

For the ‘knee injury only’ cohort, the base case DMOAD regimen increased discounted QALE by 0.03 QALYs from the standard of care (undiscounted: 0.10 QALY increase). For the ‘obese only’ cohort, the base case did not change discounted QALE and caused a decrease in undiscounted QALE by 0.01 QALYs from the standard of care. For the ‘non-obese without knee injury’ cohort, discounted QALE decreased by 0.01 QALYs from the standard of care (undiscounted: 0.03 QALY decrease).

Economic Outcomes of Pharmacologic Knee OA Prophylaxis—In the absence of any preventative regimen, discounted lifetime costs from age 27 were estimated to be $80,800 for the ‘non-obese without knee injury’ cohort (undiscounted lifetime costs: $226,200), $85,400 for the ‘obese only’ cohort (undiscounted: $239,300), $83,500 for the ‘knee injury only’ cohort (undiscounted: $234,000), and $90,400 for the ‘obese with knee injury’ cohort (undiscounted: $252,600).

The base case DMOAD regimen increased discounted lifetime costs in the ‘obese with knee injury’ cohort by $4,600 over the standard of care. For the ‘knee injury only,’ ‘obese only,’ and ‘non-obese without knee injury’ cohorts, the base case DMOAD regimen increased discounted lifetime medical costs by $7,100, $9,200, and $10,200, respectively.

Cost-Effectiveness of DMOADs for OA Prevention—Incremental cost effectiveness ratios (ICERs) for OA prophylaxis compared to no-prophylaxis for the ‘obese with knee injury’ cohort and ‘knee injury only’ cohort are shown in Table 2. For the ‘obese with knee injury’ cohort, the base case DMOAD regimen resulted in an ICER of $118,000 per QALY

gained (Figure 3). The ‘knee injury only’ cohort resulted in an ICER of $257,200/QALY (Figure 4). In the ‘obese only’ and ‘non-obese without knee injury’ cohorts, the DMOAD prevention regimen was dominated.

Sensitivity Analyses—In addition to evaluating DMOAD cost-effectiveness under base case parameters, we evaluated the regimen under a range of values for annual cost, efficacy, toxicity, and age of DMOAD initiation. The results of these sensitivity analyses for the ‘obese with knee injury’ and ‘knee injury only’ cohorts are illustrated in Figures 3 and 4 and Technical Appendix Figures 1 and 2. For both cohorts, DMOADs for OA prevention became less cost-effective under the following conditions: increasing annual DMOAD cost from $300 to $3,000, decreasing early efficacy from 70% at maximum to 30% at minimum, increasing the probability of late failure from 1% to 10%, and increasing major toxicity from no toxicity (Technical Appendix, Figures 1a and 2a) to 0.44% (Technical Appendix, Figures 1b and 2b). Because regimens priced at $3,000 were either dominated or demonstrated ICERs >$125,000/QALY in all four cohorts at all levels of toxicity and efficacy, these regimens were not shown in any figure reporting ICERs for our sensitivity analyses.

For the ‘obese with knee injury’ cohort, decreasing the annual cost of the DMOAD regimen from $1,000 in the base case to $300 decreased the ICER for this cohort to $36,800/QALY, assuming 0.22% toxicity, 5% late failure, and 40% early efficacy (Figure 3). Increasing early efficacy from 40% in the base case to 70%, assuming $1,000 annual cost and 5% late failure, decreased the ICER to $59,700/QALY. Decreasing late failure from 5% in the base case to 1% decreased the ICER to $78,400/QALY. Decreasing annual likelihood of major toxicity from the base case 0.22% to 0% reduced the ICER to $108,300/QALY. Increasing the initiation age from 50 in the base case to 60 increased the ICER to $157,300/QALY; decreasing the initiation age to 40 and 30 increased the ICER to $150,700/QALY and $166,300/QALY, respectively.

For the single risk factor cohorts, the preventative DMOAD regimen resulted in lower ICERs for the ‘knee injury only’ cohort than for the ‘obese only’ cohort overall when compared to guideline concordant care. When the DMOAD regimen had 0.22% major toxicity and was priced at $1,000 annually, the ‘knee injury only’ cohort demonstrated ICERs less than $150,000/QALY only when early efficacy was at least 50% and late failure was at most 5%. Use of the DMOAD regimen in the no risk factors ‘non-obese without knee injury’ cohort was either less effective than the standard of care or produced ICERs greater than $150,000/QALY.

A Best Case Prophylaxis—In addition to evaluating a base case DMOAD regimen, we estimated the cost-effectiveness of a ‘best case’ DMOAD regimen for the prevention of knee OA: no major toxicity, 70% early efficacy in the first year, 1% late failure in subsequent years, and an annual cost of $300. For the high risk ‘obese with knee injury’ cohort, discounted lifetime costs were $4,800 higher than for the standard of care. The ICER associated with the best case prophylaxis for this cohort was estimated at $10,700/QALY (Technical Appendix Figure 1a) when the regimen was initiated at age 30. When the best case regimen was initiated at age 60 for the ‘obese with knee injury’ cohort, discounted lifetime costs were increased by $500 and the ICER was increased to $16,500/QALY. For

the ‘knee injury only’, ‘obese only’, and no risk factors cohorts, ICERs for a best case regimen initiated at age 30 were estimated at $25,100/QALY (Technical Appendix Figure 2a), $124,600/QALY, and >150,000/QALY, respectively.

DISCUSSION

This analysis evaluated the economic and clinical impact of a regimen modeled on clinically relevant ranges for early efficacy, late failure, annual cost, and toxicity based on other pharmacologic regimens used for disease prophylaxis and OA management. While there is no clear definition for what constitutes a cost-effective medication, maximum willingness-to-pay thresholds range from $50,000/QALY to $150,000/QALY in literature from the United States[56–58]. In this report we show that the use of a DMOAD regimen to prevent knee OA may improve QALE at cost-effectiveness levels comparable to other accepted therapies when used in persons at high risk for OA. These high-risk individuals include persons with two significant risk factors for developing knee OA, such as obesity and a history of knee injury, as well as persons with one risk factor that significantly increases the risk of knee OA on its own, such as a history of knee injury. Table 2 shows ICERs for preventative therapies used for other prevalent chronic conditions. While prophylaxes for stroke, major vascular events, and cardiovascular events have lower ICERs than those for a DMOAD-based OA prevention regimen, prophylaxis for myocardial infarction and breast cancer have ICERs similar to those presented in this analysis[59,60].

DMOAD regimens priced at $3,000 per year or higher are unlikely to be cost-effective by current US standards, even for persons with two knee OA risk factors. However, for a high-risk cohort, prophylaxis is likely to be cost-effective when priced at $300 per year. Starting this DMOAD regimen at an earlier age demonstrated a tradeoff of a higher potential to delay knee OA onset alongside a higher potential for minor and major toxicities. Despite these tradeoffs, our research shows that beginning prophylaxis earlier in life increases QALE for these cohorts. Though beginning a regimen later in life may cost less, starting a prophylaxis regimen at an age after most patients are diagnosed with OA will not significantly improve QALE benefits. QALE was also moderately affected by variations in the major toxicity levels of the DMOAD regimen. The negative effect of toxicity was greater with earlier age of prophylaxis initiation, which was likely due to both the immediate negative impact of experiencing a major toxicity as well as the long-term negative effect of removing subjects from an otherwise efficacious regimen.

These results should be viewed within the context of certain limitations and assumptions underlying the analysis. Indirect medical costs were not considered in this economic analysis, although they are typically substantially more than direct costs. Furthermore, our analysis depended greatly on symptomatic knee OA incidence data. Based on our analysis, if OA incidence values were to increase, pharmacologic prophylaxis would become more cost-effective. This limitation becomes particularly important when considering our differentiation of the cohorts was based on the stratification of OA incidence rates according to the associated added risks of obesity and previous knee injury. This stratification based on the merging of two risk factors assumed that a subject at increased risk of OA due to obesity would be treated with a preventative pharmacologic regimen in the same way a subject with

history of knee injury would be. In other words, we assumed subjects reporting non-traumatic risk factors would require the same preventative measures as those reporting traumatic risk factors. Subjects with history of knee injury may have underlying OA-related disease mechanisms[61–63] that differ from those of obese subjects[64,65]. Accordingly, our use of the same preventative regimen strategy for both groups constitutes a limitation in our analysis. The analysis also focused entirely on pharmacologic methods of OA prevention rather than behavioral or surgical methods. Behavioral interventions focused on weight management and exercise have been shown in the literature to potentially reduce the risk for incident symptomatic knee OA as well as potentially slow the progression of the disease by reducing joint inflammation as well as the weight-bearing load of the joint[65–69]. Studies evaluating the economic value of these types of behavioral management strategies for knee OA prevention may accordingly serve as another useful and important focus for future research. An additional limitation to our analysis was our assumption that a single pharmacologic preventative regimen would be used. Regarding toxicity, we assumed these agents would have similar toxicities to selective NSAIDs because OA prophylaxis is still largely hypothetical. This analysis did not evaluate the possibility that pharmacologic prophylaxis may be metabolized differently in older people. Finally, the OAPol Model does not define all pathophysiological aspects of OA and focused primarily on cartilage; to fully understand the impact of prophylaxis for knee OA, it may be necessary to incorporate the broader range of pathological and mechanical problems in the affected knee[8].

To our knowledge, this is the first economic evaluation of the use of pharmacologic regimens for the prevention of knee OA. We recently published the cost-effectiveness of using DMOADs for the treatment of knee OA upon OA incidence in Losina et al[9]. In that analysis, annual cost, suspended progression of the disease, and pain relief were key drivers of the cost-effectiveness of using DMOADs as treatment for the disease. Taken together, these analyses represent critical first steps in the pre-evaluation of pharmacologic regimens that halt or reverse the structural progression of knee OA. While few economic analyses of DMOAD regimens exist in the literature, some studies have evaluated the benefits of therapies to reduce knee OA incidence, including behavioral methods leading to weight-loss and increased muscle strength around the knee[66,70]. Few studies have also evaluated the use of pharmacologic regimens for the prevention of knee OA. Recently, statins have received attention as a potential pharmacological method to reduce OA incidence and progression with mixed results[71–76]. Other recent studies have begun to evaluate biomarkers that may identify individuals at high risk for OA[77]. While research continues to investigate the efficacy of methods for OA prevention, the sum of these studies demonstrates the relevance of this and other cost-effectiveness analyses that hope to inform how policy-makers, clinicians, and patients collectively evaluate how to most effectively manage medical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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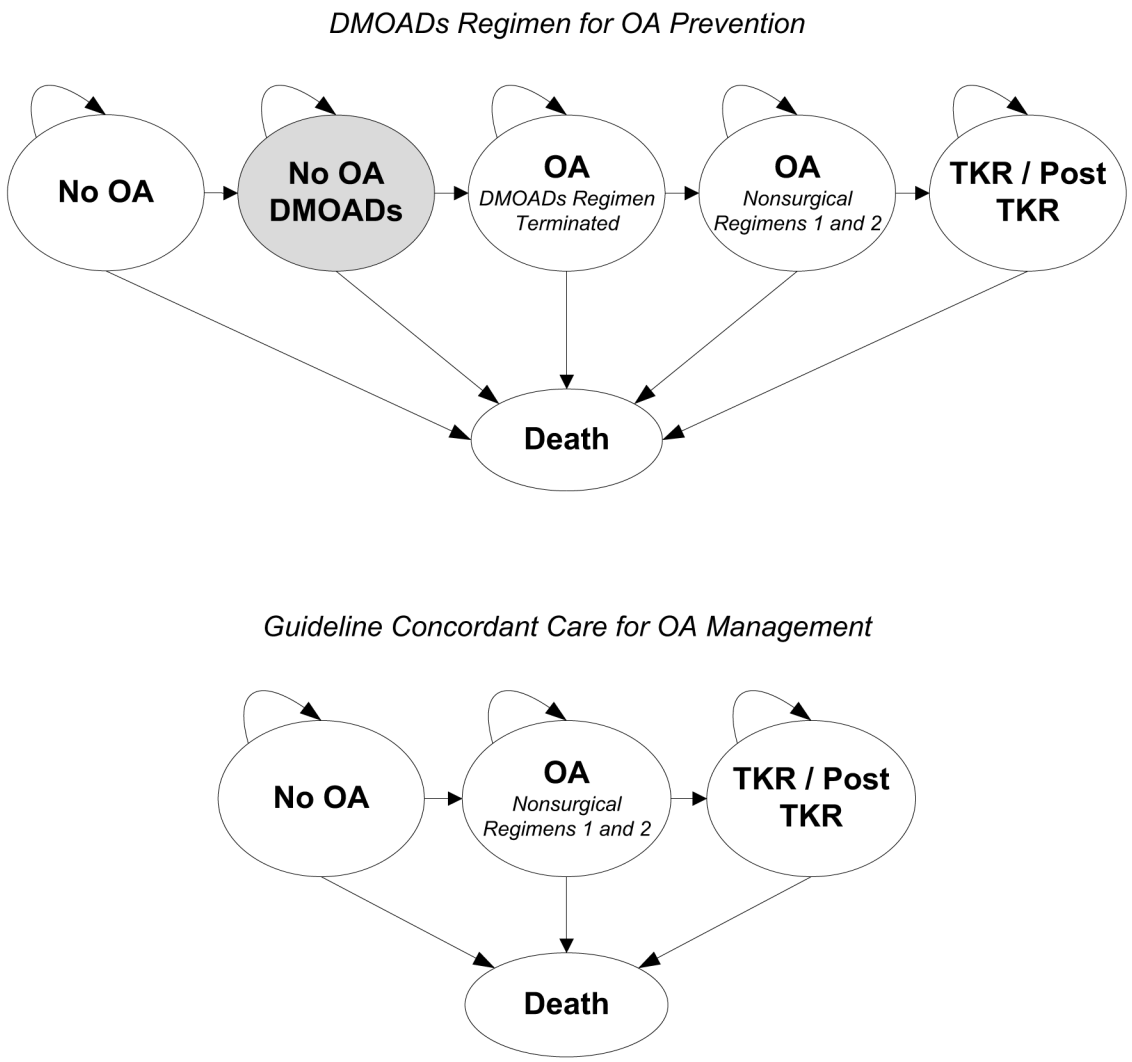

Figure 1. Sequence of OA Prevention, Incidence, and Treatment

The figure shows the sequence of health states for the prevention, incidence, and subsequent treatment of OA. Subjects who had no diagnosed radiographic evidence of OA either received a DMOAD regimen for the prevention of knee OA or received no prophylaxis. Subjects may have gone on to develop OA, at which point they underwent the standard of care for OA treatment and ceased any prophylactic regimen. Subjects then continued through the model until this guideline-concordant care culminated in the receipt of a total knee replacement.

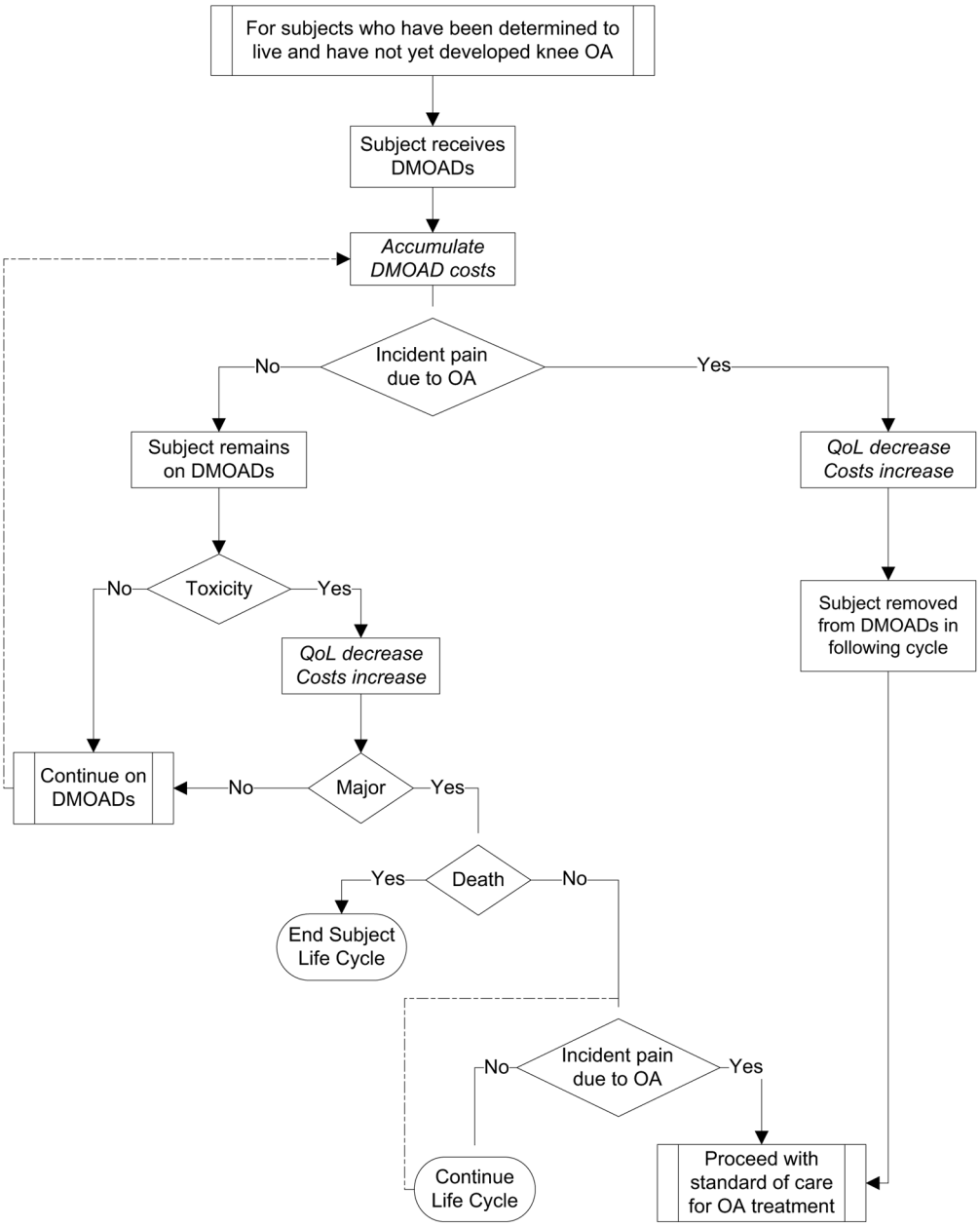

Figure 2. DMOADs as Prevention in the OAPol Model

This figure depicts the path of a hypothetical subject in the OAPol Model receiving DMOADs before the incidence of OA. If OA developed during or following the discontinuation of a prophylactic DMOAD regimen, subjects continued on with guideline-concordant OA treatment.

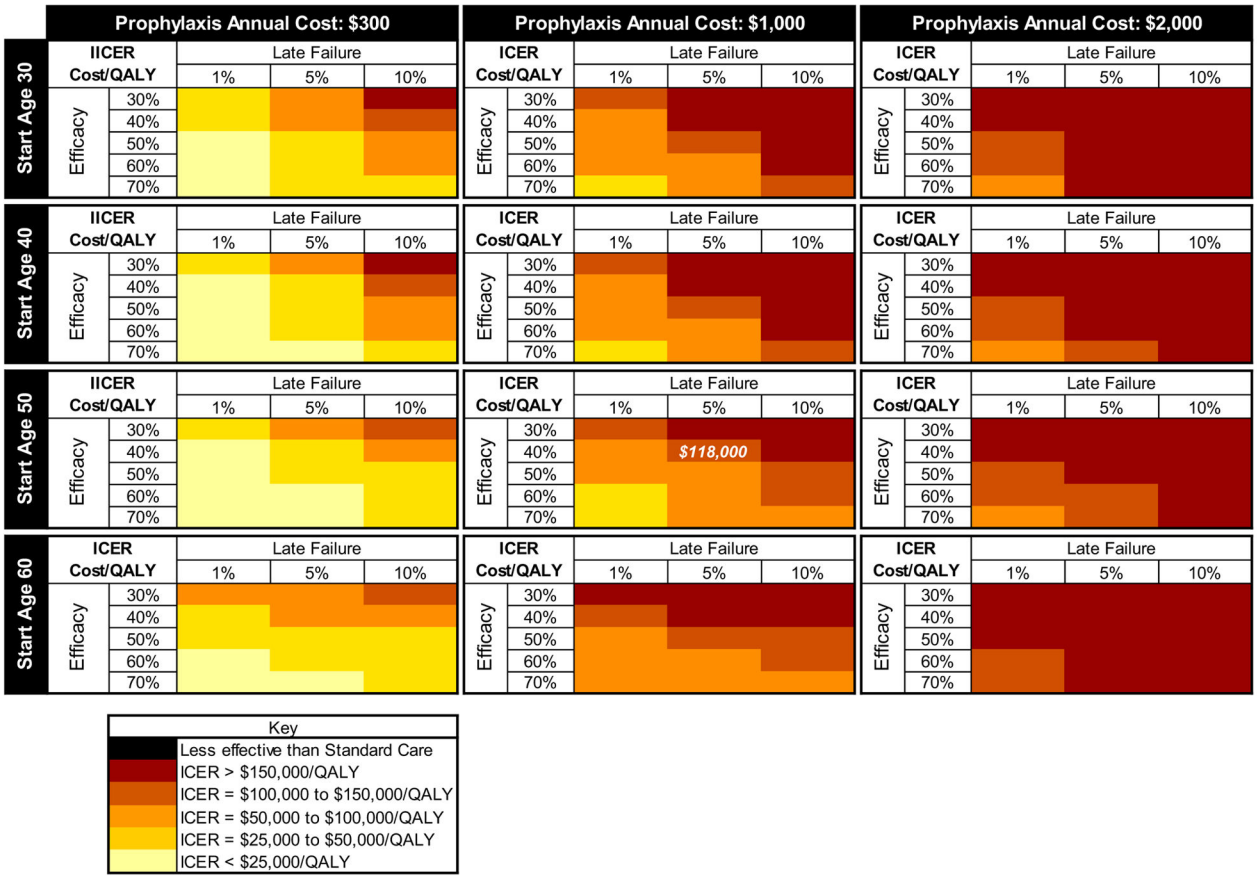

Figure 3. Incremental Cost-Effectiveness Ratios of DMOADs as Prevention: 'Obese with knee injury' Cohort; Prophylaxis with 0.22% Major Toxicity

The 'Cost' column headers apply to every row below them. The 'Start Age' row headers on the left of the figure apply to all columns in that row. This figure applies to DMOADs with major toxicity of 0.22%. ICERs improved with increasing efficacy and decreasing toxicity, cost, and late failure. ICERs also improved with increasing start age from initiation at age 30 up to initiation at age 50; ICERs were less favorable at a start age of 60, likely because this was after average age of knee OA onset had been reached. The ICER estimated for the base case DMOAD regimen is highlighted.

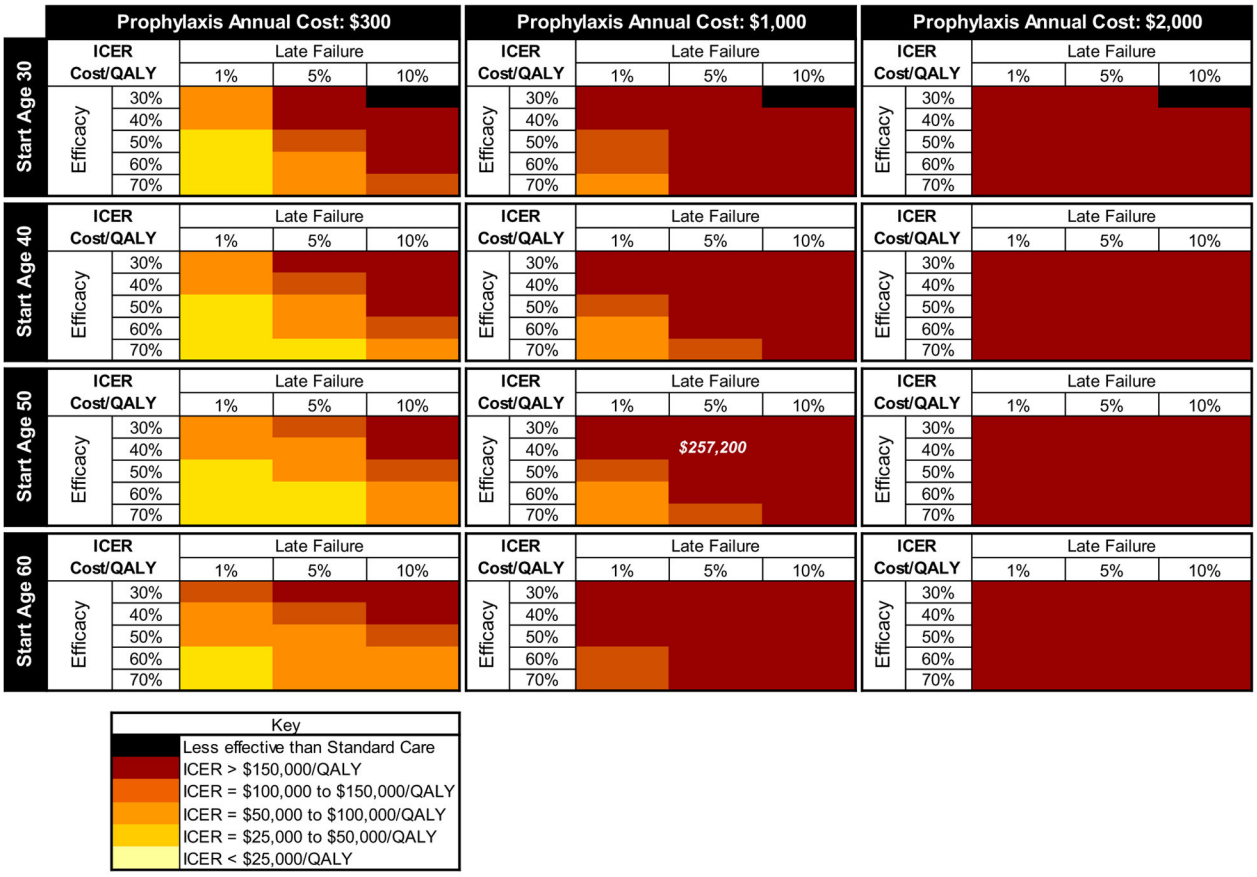

Figure 4. Incremental Cost-Effectiveness Ratios of DMOADs as Prevention: 'Knee Injury Only' Cohort; Prophylaxis with 0.22% Major Toxicity

Like Figure 3, this figure illustrates the ICERs estimated for a DMOAD regimen at 0.22% major toxicity for the 'knee injury only' cohort. ICERs were worse for this cohort than for the 'obese with knee injury' cohort. Prophylaxis was unlikely to have ICERs of less than $150,000 when the annual cost of the drug was $2,000 or greater. The ICER estimated for the base case DMOAD regimen is highlighted.

Table 1

Model Input

Parameter (applied annually)	Overall Estimates								Sources
Cohort Characteristics									
Incidence of knee OA (annual %)	**'No Risk Factors' Cohort**		**'Obese Only' Cohort**		**'Knee Injury Only' Cohort**		**'Obese with Knee Injury' Cohort**		
Age Groups	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	
25 – 34	0.09	0.12	0.16	0.29	0.78	0.84	1.28	2.05	Wilder et al. 2002[12] NHANES 2003–2004[28] Losina et al. 2013[28]
35 – 44	0.10	0.13	0.16	0.31	0.85	0.90	1.28	2.21	
45 – 54	0.15	0.23	0.30	0.41	1.24	1.66	2.50	2.93	
55 – 64	0.27	0.38	0.49	0.79	2.20	2.72	4.02	5.55	
65 – 74	0.19	0.25	0.29	0.35	1.57	1.80	2.38	2.48	
75 – 84	0.17	0.18	0.23	0.30	1.37	1.28	1.86	2.16	
85+	0.17	0.18	0.23	0.30	1.37	1.28	1.86	2.16	
Quality of Life Utilities									
All subjects with severe OA (K-L 3 or 4)	0.690								
Age Groups	**Non-Obese Number of Co-morbidities**				**Obese Number of Co-morbidities**				
No Knee Pain	**0 – 1**	**2 – 3**	**4 – 5**		**0 – 1**	**2 – 3**	**4 – 5**		
25–44	0.955	0.903	0.662		0.921	0.870	0.662		NHANES 2005–2006[17] NHANES 2007–2008[18]
45–64	0.952	0.901	0.662		0.918	0.867	0.662		
65+	0.943	0.891	0.662		0.909	0.858	0.662		
Knee Pain									
25–44	0.814	0.721	0.662		0.781	0.688	0.662		
45–64	0.806	0.713	0.662		0.773	0.679	0.662		
65+	0.884	0.791	0.662		0.850	0.757	0.662		
Annual Direct Medical Costs* (in 2010 USD)									
Age Groups	**0 – 1 Co-Morbidities**		**2 – 3 Co-Morbidities**		**4 – 5 Co-Morbidities**				NHANES 2005–2006[17] NHANES 2007–2008[18] Pope et al. 2004[25]

Parameter (applied annually)		Overall Estimates		Sources
25–34	$1,302	$6,652	$12,506	
35–44	$1,814	$7,165	$13,019	
45–49	$2,431	$7,755	$11,751	
50–54	$2,432	$7,755	$11,751	
55–59	$3,239	$8,232	$12,902	
60–64	$3,940	$8,933	$13,602	
65–69	$4,198	$8,856	$15,366	
70–74	$4,888	$9,547	$16,056	
75–79	$5,712	$10,371	$16,881	
80+	$7,505	$12,163	$18,673	

DMOAD Characteristics		
	Base Case Values	***Ranges Considered in Sensitivity Analyses***
Treatment Efficacy in the First Year	40%	30% – 70%
Failure of Treatment in Subsequent Years	5%	1% – 10%
Minor Toxicity: First Year (Subsequent Years)	9.50% (7.27%)	(not varied)
Major Toxicity**	0.22%	0% – 0.44%
Annual Cost	$1,000	$300 – $3,000
Age at which subjects begin taking DMOADs	50	30, 40, 50, 60

* This excludes pain management. Acknowledging that patients may use analgesics to control painful knee OA, an annual cost of $203.80 was added for patients with symptomatic knee OA[26,27].

** Major toxicity values were based on reported toxicity of selective NSAIDs (0.44% incidence, 10% mortality)[34].

Abbreviations: OA, osteoarthritis; K-L, Kellgren-Lawrence grade; NHANES, National Health and Nutrition Examination Survey; USD, United States Dollars; DMOAD, disease-modifying osteoarthritis drug

Table 2

Incremental Cost-Effectiveness Ratios for Base Case DMOADs and other Preventative Regimens for Chronic Disease

Disease	Target population		*Prophylaxis*	ICERs*	Source
Knee Osteoarthritis	Patients who are obese and have a history of knee injury		*Base Case DMOAD***	$118,000	
	Patients who are non-obese and have a history of knee injury			$257,200	
	Patients who are obese and have no history of knee injury			*dominated*	
	Patients who are non-obese and have no history of knee injury			*dominated*	
	Non-Osteoarthritis Chronic Diseases				
Breast cancer	Women who were at a higher risk of breast cancer	ages 35 to 49 ages 50 to 59 ages 60 to 69	*Tamoxifen*	$68,500 $113,200 $124,100	Noe et al. 1999[59]
Cardiovascular Events	Patients over 35 years of age with coronary disease		*Aspirin Clopidogrel*	$16,400 $46,200	Gaspoz et al. 2002[78]
Major Vascular Events (MVE) ***	Patients aged 55 with blood total cholesterol concentrations ≥ 135mg/dL and medical history of coronary disease, cerebrovascular disease, other occlusive arterial disease, diabetes mellitus, or treated hypertension	5-year MVE risk at initiation of treatment: 5% 5-year MVE risk at initiation of treatment: 40%	*Simvastatin*	$23,300 $5,300	Heart Protection Study Collaborative Group 2009[79]
Myocardial Infarction	Patients with past myocardial infarction (mean age 62.3 years)		*Amiodarone* *Implantable Cardioverter Defibrillator*	$103,100 $181,000	Sanders et al. 2001[60]
Stroke	Patients 65 years of age with nonvalvular atrial fibrillation and one additional risk factor		*Warfarin sodium*	Cost-saving	Gage et al. 1995[80]

* ICERs reported as incremental costs in 2010 USD per QALY gained compared to guideline concordant care. ICERs are rounded to the nearest $100/QALY.

** Base Case DMOADs were initiated at age 50, had a 40% probability early efficacy, 5% probability of late failure, annual cost of $1,000, and posed a 0.22% risk of major toxicity.

*** For example, a nonfatal myocardial infarction or coronary death, any stroke, or revascularization procedure.

Abbreviations: ICERs, incremental cost-effectiveness ratios; DMOAD, disease-modifying osteoarthritis drug.